REMARKS

Claims 1-4 and 6-13 are currently pending in the application. Claims 1, 3, 8, 10, and 12 are in independent form.

Applicant has amended claims 1, 8, 10, and 12 to include the step of "identifying increased numbers of new neurons." Support for this amendment can be found on page 10, lines 11-12 ("Increased numbers of new neurons were identified when this compound was administered at and beyond 24 hours after onset of stroke.") No new matter has been added.

Claims 1-13 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that isolation and culture of mesenchymal stem cells is disclosed as well as how phosphodiesterase inhibitors can be used to promote neurogenesis in rats, but not a patient in need of neurogenesis. The Office Action holds that there is no mention of how mesenchymal stem cells can be used to promote neurogenesis to a patient in need of neurogenesis promotion, and there are also no working examples of stem cells combined with a phosphodiesterase inhibitor promoting neurogenesis of increasing neurological function.

In response thereto, Applicant and others have demonstrated that ischemic stroke induces neurogenesis in the adult rat and mouse (see references listed herein - Zhang, et al. (2001); Jin, et al. (2001); Parent, et al. (2002); Arvidsson, et al. (2002); Zhang, et al. (2004)). Stroke-induced neurogenesis has also recently been demonstrated in the adult human brain, even in advanced age patients (Macas, et al. (2006); Curtis, et al. (2007)). Transplantation of rodent or human mesenchymal stromal cells (MSCs) substantially enhances neurogenesis and improves

neurological functions after stroke in the rat (Chopp, et al. (2002); Chen, et al. (2003)). Based on these data, Applicant predicted that administration of MSCs promotes endogenous neurogenesis in stroke patients. Although there are no data showing that MSCs enhance neurogenesis in human patients, clinical trials in humans with stroke and spinal cord injury show that intravenous administration of bone marrow cells or direct transplantation of autologous whole bone marrow into the site of spinal cord injury improves neurological function significantly improves neurological function after stroke and spinal cord injury, respectively. (Park, et al. (2005); Bang, et al. (2005)).

Rat models of disease are widely employed for the development of many treatments. It is thus accepted methodology for one skilled in the art of neurogenesis to use the rat model of Applicant and apply results of the rat model to humans. Modern medical science emerges from the laboratory and from animal models of disease. Reconsideration of the rejection is respectfully requested.

Claims 1, 3, 5-8, 10, and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,075,028 to Graham. Specifically, the Office Action holds that Graham discloses a method of using a phosphodiesterase, sildenafil, to treat Tourette's syndrome and other related central nervous system (CNS) disorders. Promotion of neurogenesis and increasing neurological function would inevitably be involved by this treatment, since someone having Tourette's would be in need of neurogenesis promotion. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Graham, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Graham discloses that sildenafil transiently reduces neurological symptoms of Tourette's syndrome because the symptoms return when administration of sildenafil is ceased. Graham does not provide any mechanisms underlying the effect of sildenafil on reduction of the symptoms. Nowhere in Graham is there any statement or inference to neurogenesis in the brain and brain plasticity. Applicant's data demonstrate that sildenafil enhanced-neurogenesis and functional outcome persist for at least 20 days after termination of the use of the drug (Zhang, et al. (2002)). Doses of sildenafil used in Applicant's studies are 2, 5, and 10 mg/kg, which are higher than doses used in Graham. In addition, Applicant demonstrates that agents which increase cGMP levels such as sildenafil act directly on neural progenitor cells in brain to induce the production of new neural cells (Zhang, et al. (2002); Wang, et al. (2005); Chen, et al. (2003); Chen, et al. (2005); Chen, et al. (2006); Lu, et al. (2007); Zhang, et al. (2005); Zhang, et al. (2006)). Tourette`s syndrome is not a form of neural injury where cerebral tissue is infarcted. In Tourette`s, there are no neurological deficits, only abnormal behavior, in sharp contrast to stroke. Treatment of stroke with sildenafil evokes neurogenesis and brain remodeling, mechanisms of action which cannot be inferred by the transient amelioration of behavioral symptoms present in Tourette`s patients.

Applicant has further amended the independent claims to positively set forth method steps requiring promoting neurogenesis, augmenting production of neurons, and increasing neurological and cognitive function in the patient to which the phosphodiesterase inhibitor is administered. Further, independent claim 3 requires an effective amount of a phosphodiesterase inhibitor sufficient to promote neurogenesis. Applicant has also amended the independent method claims to require the step of "identifying increased numbers of new neurons". Graham does not disclose any of the required method steps and certainly does not disclose an amount of sildenafil that can promote neurogenesis.

Applicant notes that no cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, *Graham cannot perform the required steps of claims 1, 8, 10, and 12 of "identifying increased numbers of new neurons".*

Therefore, since the Graham patent does not disclose promoting neurogenesis with a phosphodiesterase inhibitor or identifying increased numbers of new neurons as set forth in the presently pending independent claims, the claims are patentable over the Graham patent and reconsideration of the rejection is respectfully requested.

Claims 3 and 4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,827,740 to Pittenger. Specifically, the Office Action holds that Pittenger claims a composition of stem cells and a phosphodiesterase inhibitor. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Pittenger, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Pittenger discloses a method of directing MSCs to differentiate into adipocytes by treating them with glucocorticoid and a compound that elevates cAMP, i.e. a phosphodiesterase inhibitor. Adipose tissue is used as energy storage and releases fatty acids when a person does not take in enough calories. Pittenger does not disclose anything about neurogenesis. The phosphodiesterase inhibitor of Pittenger is merely used to differentiate the MSCs, not for actual treatment of the patient. Thus, Pittenger does not disclose an effective amount of a phosphodiesterase

inhibitor to promote neurogenesis. The effective amount for promoting neurogenesis is different from that required to be an effective amount for inducing adipogenic differentiation.

Therefore, since the Pittenger patent does not disclose a compound for promoting neurogenesis comprising an effective amount of a phosphodiesterase inhibitor sufficient to promote neurogenesis as set forth in the presently pending independent claim, the claim is patentable over the Pittenger patent and reconsideration of the rejection is respectfully requested.

Claims 1-13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Graham in view of International Patent Application Publication No. WO/2000/050568 to Price. Specifically, the Office Action holds that Graham teaches treating Tourette's syndrome by administering sildenafil. Since someone having Tourette's syndrome would be in need of neurogenesis promotion, the Office Action holds that it meets this limitation. The Office Action holds that neurotransmission dysfunction is implicated with Tourette's, and Alzheimer's is also associated with neurotransmission dysfunction. The Office Action also holds that Price discloses a method of promoting neurogenesis or increasing neurological function (since they treat Alzheimer's) that includes cellular therapy. Therefore, the Office Action holds that it would have been obvious for one skilled in the art to use the cellular therapy of Price with the sildenafil of Graham. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over Graham in view of Price is respectfully requested.

"Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This

requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).

There is no reason why one skilled in the art would combine Graham and Price. Graham is concerned with Tourette's syndrome and symptoms, regardless of whether other diseases are mentioned. As stated above, in Tourette's, there are no neurological deficits, only abnormal behavior, in sharp contrast to stroke dealt with in the present invention. Treatment of stroke with sildenafil evokes neurogenesis and brain remodeling, mechanisms of action which cannot be inferred by the transient amelioration of behavioral symptoms present in Tourette's patients. Thus, if anything, Graham is comparing the symptoms of Tourette's to some similar symptoms of Alzheimer's. A Tourette's patient is not in need of neurogenesis, thus one would not use the stem cells of Price to treat damaged brain. In contradistinction, the presently pending claims relate to promoting neurogenesis and provide new neural growth, along with tissue growth from cellular therapy as well as requiring the step of identifying increased growth of new neurons. As stated above, Graham cannot perform the required steps of claims 1, 8, 10, and 12 of "identifying increased numbers of new neurons". Therefore, it would not be obvious to combine Graham and Price to arrive at the present invention as claimed in the presently pending independent claims.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

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